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SYMPOSIUM OVERVIEW

An Update on Exposure and Effects of Lead

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Lead is perhaps the oldest of industrial toxins, dating back to Roman times. Despite the historic knowledge of lead, this metal remains a public health concern today. This is due both to the pervasiveness of lead in the environment and to the awareness of toxic effects of lead occurring at exposure levels lower than previously thought harmful.

At the 1991 Annual Meeting in Dallas, Texas, the Society of Toxicology hosted the symposium: "An Update on Exposure and Effects of Lead." The goal of the symposium was to present an overview on critical issues associated with lead toxicity—ranging from fundamental mechanisms, such as the role of lead binding proteins, to assessment of the potential effectiveness of lead abatement measures, such as the impact on blood lead of home deleading. These issues are summarized in Fig. 1 using the four-stage paradigm of risk assessment as described by the National Academy of Science (NRC, 1977). Clearly, understanding potential impacts of lead in humans is interdisciplinary, involving the efforts of toxicologists, pathologists, epidemiologists, environmental chemists, and others.

The following is a summary of each of the individual presentations.

Role(s) of Lead-Binding Proteins (PbBP) in the Renal and Neurotoxic Effects of Lead in the Rat (B. A. Fowler, University of Maryland at Baltimore)

The kidney and brain are major target organs for lead toxicity but the molecular factors which mediate the low-dose effects of this metal in these tissues are not currently understood. Knowledge of these molecules greatly facilitates understanding of the mechanisms of lead toxicity and explains why only certain cells in these target organs are affected.

Studies of these molecules may also provide information to explain age- and sex-related differences in lead toxicity. Comparison of these molecules between experimental animal model systems and human tissues should also greatly facilitate animal-human risk extrapolations and provide a means for explaining known differences in human susceptibility to lead.

Renal lead-binding proteins (PbBP). Early studies by Moore and Goyer (1974) showed that lead intranuclear inclusion bodies from rats exposed to high doses of lead contained a protein rich in aspartic and glutamic amino acids with an approximate molecular mass of 27,000 Da. Subsequent studies by Oskarsson *et al.* (1982) demonstrated the presence of two lead-binding components in rat kidney cytosol with estimated molecular masses of 11,500 and 63,000 Da and that the *in vivo* binding pattern appeared to shift to the 63,000-Da component with time, suggesting a possible aggregation phenomenon involving the lower molecular weight component. Other studies by Shelton and Egle (1982) demonstrated an acidic carboxyl-rich nuclear protein from rat kidneys which had an estimated molecular mass of 32,000 Da. The importance of the above studies is in providing an information base from several laboratories which clearly indicates that lead is bound by chemically similar molecules found in both the cytosol and nucleus. Further studies (Goering and Fowler, 1984, 1985; Goering *et al.*, 1986) demonstrated that the cytosolic lead-binding components bound zinc and were capable of both attenuating the inhibitory effects of Pb^{2+} on the heme biosynthesis pathway enzyme δ-aminolevulinic acid dehydratase (ALAD) and facilitating the cell-free nuclear translocation of Pb and chromatic-binding of Pb as judged by KCl extraction procedures (Mistry *et al.*, 1985, 1986). These data are consistent with the hypothesis (Fowler, 1989) that the PbBP acts as a tissue-specific receptor for Pb which is capable of mediating the well-known alterations in renal gene expression (Fowler *et al.*, 1985) produced by lead exposure. More recent studies (Fowler and DuVal, 1991) have identified the renal PbBP as the kidney-specific cleavage producer of α2μ-globulin which is minus the first 9 N-terminal residues (Eckstrom, 1983; Swenberg *et al.*, 1989). These studies also demonstrated that the protein aggregates under conditions of elevated Pb exposure. Preliminary Western-blot analyses utilizing a polyclonal antibody to this protein (Racine *et al.*, 1988) demonstrated that the protein was present in nuclear KCl

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Use of Site-Specific Data in Models for Lead Risk Assessment and Risk Management (A. H. Marcus, Battelle Applied Statistics and Data Analysis Section)

The concentration of lead in whole blood is presently accepted as the best index of body lead burden, and thus the best indicator of the reduction of population exposures to lead from abatement programs. Computer models for predicting changes in blood lead distribution over time for children of various ages have been developed by USEPA and USCDC. These models can be adapted to site-specific risk assessments for lead, if the following data are available: (1) characterization of distribution of lead levels in diverse media to which children have been exposed since conception, including air, water, soil, house dust, paint, and food; (2) characterization of factors that affect biological availability of lead, including age of child, chemical speciation, particle size, and dietary cofactors; (3) demographic and socioeconomic factors that affect amount of childhood lead exposure, including age of children, parental involvement and supervision, and frequency of outdoor play; (4) environmental factors that may alter lead biokinetics, such as inadequacies in calcium or iron nutrition; (5) characterization of changing time patterns of environmental lead following proposed abatement. Sensitivity of the model parameters will be demonstrated for three scenarios of current regulatory interest: soil lead abatement for lead smelter and mining communities, water lead abatement by control of the corrosivity of water, and paint lead abatement in occupied dwelling units.

The toxicity of the metal lead and its compounds was known to the ancient Greeks and Romans, and lead is still one of the most important modern environmental toxicants. The concentration of lead in whole blood is the most commonly used index of internal lead absorption. The most sensitive population groups include young children and the fetus. The effectiveness of lead abatement programs can be judged by their ability to reduce lead levels in lead-poisoned children and in preventing excessive blood lead levels in previously unexposed children. We have developed computer programs that predict population risk from childhood lead exposure and risk reduction from lead abatement measures.

A large number of individuals have assisted in the development of these models. The lead model being used by the U.S. Environmental Protection Agency (USEPA) was based on studies in infant and juvenile baboons carried out by N. Harley, T. Kneip, and P. Mallon at New York University (Mallon, 1983; Harley and Kneip, 1985). An expanded version of their model incorporating air, dust, and soil lead exposures over childhood was developed for USEPA's Office of Air Quality Planning and Standards from 1986 to 1990. The model was validated using a cross-sectional study of children in the lead smelter community of East Helena, Montana (CDC, 1986a). The validation studies are described by Johnson and Paul (1986), Marcus and Cohen (1988), and in the USEPA staff paper Exposure Analysis and Methodology Validation (1989). A greatly revised and expanded model was needed for other applications, however.

The successfully validated model was reprogrammed and expanded to include fetal exposure, nonlinear kinetics for plasma/red cell partition and for gut absorption, and a much greater variety of time-varying lead exposure sources (Cohen *et al.*, 1990). This model was provided by the USEPA Environmental Criteria and Assessment Office for preliminary

testing by USEPA staff and contractors. A user-friendly interface has been developed (Diamond, 1990), allowing even inexperienced analysts to use the program. The unexpectedly wide acceptance and applicability of this model has created a much greater need to examine the conditions under which the model can be appropriately used.

Methods

Biological foundations of the model. Lead is a multimedia, multipathway toxicant. It is first necessary to model total lead exposure through all media and from all sources, accounting for the natural age-dependent variability in exposure pattern and metabolism. Lead is absorbed through the gut and the lungs. There is evidence that absorption of lead through the gut is kinetically nonlinear, with a relatively constant passive diffusion process and a saturable facilitated diffusion process both occurring (Aungst and Fung, 1981). Particle size and chemical species may also affect gut absorption (Barltrop and Meek, 1979; Steele *et al.*, 1990). Behavioral factors such as the times between lead ingestion and meals are very important, since retention of dissolved lead salts in adults may range from 2% when taken with meals, up to 60% when taken between meals (James *et al.*, 1985). Lead uptake in infants and children appears to be much higher (Ryu *et al.*, 1983; Marcus, 1990). Dietary cofactors such as calcium, zinc, iron, and phytate may also greatly modify lead retention.

The lead model (known as the Integrated Exposure, Uptake, and Biokinetic Model for Lead, or IEUBK model) is a partially physiological compartmental model shown in Fig. 5. This model relates lead exposure by pathway to lead absorbed into the plasma. Once in the plasma, lead is distributed to other soft tissue and hard tissue pools, mainly according to a first-order kinetic model. There appears to be a saturable lead-binding capacity of the red blood cells, however (Marcus, 1985c). The whole-blood lead pool includes both plasma and red blood cells, but the plasma pool is part of a larger labile pool that includes some extracellular fluid. This is based on the excellent stable lead isotope studies of Rabinowitz *et al.* (1976) that suggest the volume of distribution of lead in blood is about 1.7 times larger than blood volume. All organ and pool sizes accurately represent pre- and postnatal child development and growth. Transit times are allometrically scaled from adults (Marcus *et al.*, 1985a,b,c; Bert *et al.*, 1989) or infants (Harley and Kneip, 1985). Fetal lead exposure is assumed to come completely from maternal blood, adjusted for a constant fractional reduction corresponding to the average ratio of umbilical cord blood lead to maternal blood lead at birth of about 0.85 (Cohen in USEPA, 1989).

Exposure of young children by various environmental pathways. Young children absorb lead from food and water. Toddlers may also ingest substantial quantities of lead from soil and dust particles that adhere to their fingers and are consumed during hand-to-mouth contact. This is a very normal part of a child's exploration of his or her world during ages 1 to 4 years. Some children have a much greater propensity to ingest nonfood objects, and this abnormal condition called *pica* may be related to calcium deficiency or emotional stress. There is little doubt that soil and dust ingestion are important pathways. Some children directly consume chips or flakes of lead-based paint from deteriorating surfaces, over and above the ingestion of fine paint particles in soil and dust (Yaffee *et al.*, 1983). Lead toxicity from ethnic foods; water supplies contaminated by lead

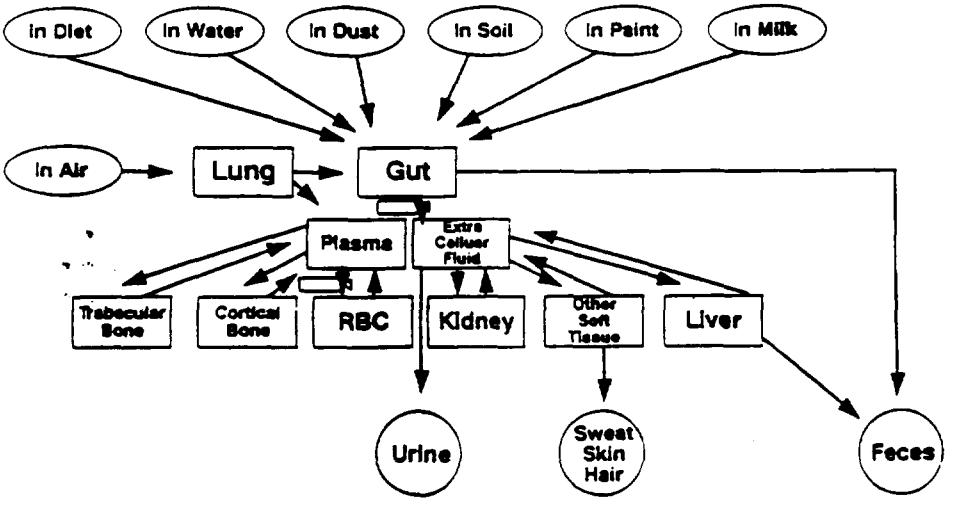

FIG. 5. Compartmental model for biokinetic component of lead cohort model. Ovals represent lead sources. Circles represent routes for elimination of lead from the body. Rectangular blocks represent compartments of the body of the child.

TABLE 3
Daily Intake of Soil and Dust Estimated from Elemental Abundances

Study	Element	Lead intake (mg/day) Median	Mean	Maximum
Davis *et al.* (1991)	Al	25	39	904
	Si	59	82	535
	Ti	81	246	6182
Calabrese *et al.* (1989)	Al	30	154	4929
	Ti	30	170	3597
	Y	11	65	5269
	Zr	11	23	838
Binder *et al.* (1986)	Al	121	181	1324
	Si	136	184	799
	Ti	618	1834	17076
Clausing *et al.* (1987)	Al	92	232	979
	Ti	269	1431	11620

leached from lead solder, pipes, or brass faucets; and lead from some folk medicines are still present in the U.S. The phasedown of leaded gasoline has eliminated air lead exposure as a major source in general, but air lead may still pose a hazard around some smelters and industrial plants. Lead exposure during lactation has not yet been included in the model.

The amount of water consumed by young children in the U.S. has been well determined by a recent survey (Ershow and Cantor, 1989). Median tap water intakes increased from 240 ml/day in infants to 731 ml/day in 7 to 10 year olds, but 90th percentile intake levels are two to three times larger, so some children are at particular risk for excessive lead exposure from water. One of the most important areas of uncertainty in exposure is in the amount of dust and soil that children consume per day. Estimates based on elemental abundances for several studies are shown in Table 3. Again, some children consume 10 to 20 times as much dust as the typical child. It is also clear that the amount of dust consumed by a child depends on the amount of dust in his or her environment and that children in dirtier environments eat more dirt (Table 4). We are not able to quantify these differences as well as we would like, but the default value of 100 mg/day suggested in the USEPA lead models is at worst slightly conservative for a typical child, and may greatly underestimate the exposure for higher risk children.

TABLE 5
Postabatement Geometric Mean Lead Levels at the Tap in Four Water Systems following pH/Alkalinity Adjustment (micrograms lead per liter)

City	Preabatement	Postabatement 1–6 months	1–2 years	>2 years
Bennington, VT	79.8	33.8	27.6	9.78
Boston, MA	57.9	29.5	11.4	9.61
Seattle, WA				
Cedar River	3.84	1.98	1.91	1.88
Tolt River	2.74	1.82	2.35	1.75

Source. Marcus and Bernholc (1990).

Characterizing the effectiveness of lead abatements. Most lead abatements change over time. Traditional paint lead abatements (sanding and burning) turn large quantities of surface paint into respirable fine particles that are distributed throughout the house and may greatly increase the lead exposure of the residents. Excessive dust lead loadings from paint removal tend to decrease to near-equilibrium levels over intervals of 2 to 6 months (Farfel, 1991, personal communication). Similarly, we would expect that cleaning household dust after soil lead remediation would be partially offset over some months as the household interior is recontaminated from remaining sources of air and soil lead, and from secondary occupational and hobby exposures. Thus the initial effectiveness of remediation may be partially offset by later recontamination, although still well below the preabatement dust levels. Data on the long-term effectiveness of

TABLE 4
Soil and Dust Intake Depends on the Environment

Sampling group	Age	Geometric mean intake (Al, Si, Ti)
Day care center (good weather)	1–2	33–88
Day care center (rainy weather)		0–19
Campgrounds		150–200
Day care center (good weather)	3+	12–62
Day care center (rainy weather)		0–29
Campgrounds		31–81

Source. Van Wijnen *et al.* (1990).

TABLE 6
Structural Equation Model Comparisons for Three Studies: Regression Coefficients for Blood Lead

Variables	Kellogg	E. Helena	Midvale
Soil lead (mg/g)	0.34	2.24	3.05
	(0.16)	(0.79)	(0.89)
Dust lead + dust lead* mouths all (mg/g)	2.14	1.54	1.55
	(0.85)	(0.51)	(0.58)
Dust lead* mouths all (mg/g)	0.92	0.94	1.55
	(0.36)	(0.31)	(0.58)
Age 1	−5.72	−0.34	−1.74
	(1.77)	(1.02)	(0.57)

urban soil lead remediation are being collected in USEPA's Three-City Superfund Soil Lead Abatement Demonstration Project, with results expected by mid-1992. Since soil and paint lead remediation will be applied only to sites with the highest lead levels, it is absolutely inappropriate to characterize the effectiveness of soil lead abatement or paint lead abatement by use of mean values. A more accurate approach, using disaggregate intervention data, is illustrated below.

Water lead control by reducing water corrosivity should become more effective over time, since passivating layers on exposed lead solder, fittings, and pipes are expected to grow with longer duration of treatment. This is clearly illustrated by data on some houses with lead plumbing systems in Bennington and Boston, and on a general sample of houses in Seattle, shown in Table 5.

Statistical inferences about environmental lead pathways. In some cases there is very useful information about the direct and indirect pathways of lead from various sources to children. A sophisticated statistical approach to lead pathway modeling was developed by Bornschein *et al.* (1985, 1988, 1990) and applied to cross-sectional blood lead and environmental lead data in Cincinnati, Ohio, Telluride, Colorado, and Midvale, Utah. We have used a different and more robust method of covariance structure modelling in applications to data from Kellogg, Idaho, East Helena, Montana, and Midvale, Utah (Marcus, 1990b). Our results are shown in Table 6. These results show very clearly that the amount of lead uptake from household dust, and from household dust adjusted by relative frequency of mouthing behavior, are statistically identical in three very different types of communities. Kellogg had a very active primary lead smelter that had been closed for two years when the 1983 CDC study was carried out. The primary lead smelter in East Helena was still active, however. The lead smelters and metal processing plants in Midvale had been inactive for many years but lead was present in large tailings piles and as yard fill soil in many households. In spite of these source differences, *the biological availability of lead in household dust was almost the same at all sites studied.*

The direct regression coefficient for soil lead was significantly smaller at the Kellogg site than at the other two sites. The reasons are not obvious, but plausible hypotheses exist; for example (1) gut absorption of lead in soil particles may be lower because of physical or chemical properties of the particles; or (2) intake of soil lead may be lower because of differences in child behavior, such as greater parental supervision of child play or voluntary avoidance of lead-contaminated soils because of better community information. The lower *direct* uptake of soil lead in Kellogg does not alter the fact that soil lead is a potential reservoir of household dust lead. These analyses show that site-specific differences do exist and may require specific adjustments of model parameters.

TABLE 7
Comparison of Estimated Blood Lead GSD for Children in Some Smelter and Mining Towns

Study	G mean	GSD	
		Raw	Adjusted
Kellogg, ID. 1974 (Yankel *et al.*, 1977)	34.0	—	1.30
Kellogg, ID. 1983 (CDC, 1986)	14.8	1.72	1.60
Kellogg, ID. 1988 (Jacobs, 1989)	8.4	1.72	—
E. Helena, MT. 1983 (CDC, 1986)	8.8	1.67	1.53
Leadville, CO. 1987 (Chappell *et al.*, 1990)	8.7	1.79	1.63
Telluride, CO. 1986 (Bornschein *et al.*, 1988)	6.1	1.70	1.49
Midvale, UT. 1990 (Bornschein *et al.*, 1990)	5.1	1.77	1.62

Variability in human response to environmental exposures. Even if all of the children in a neighborhood were exposed to exactly the same level of environmental lead, there would be substantial interindividual differences in consumption, absorption, and elimination of lead. In practice, the distribution of blood leads for a fixed set of lead exposure values is almost always log-normal, and the shape (relative spread) of the distribution is characterized by the geometric standard deviation (GSD),

$$\text{GSD} = \exp(\text{standard deviation of } \ln(\text{blood lead})),$$

which is a dimensionless shape parameter >1. The default value used by USEPA, based on the nationwide NHANES II survey, is 1.42. Our studies suggest that a much larger value is appropriate to U.S. communities where present blood lead levels are much lower than in the past, and where a diversity of sources of roughly comparable magnitude tend to increase the variability around the predictions of the IEUBK model. This is illustrated in Table 7. The raw GSD is simply based on the variability of the whole data set, including differences in environmental lead variables, and so tends to overestimate the GSD that should be used in the IEUBK model. The adjusted GSD is the GSD for the residual deviations in ln(blood lead) after statistical adjustment for all known exposures, thus must be a minimal estimate of variability. The adjusted GSDs are all much larger than 1.42 for all cases with geometric mean blood lead less than 15 μg per deciliter. A value of 1.65 or 1.66 fits neatly between the maximal raw GSD and the minimal adjusted GSD in all cases, and we have used GSD = 1.66 in the subsequent examples.

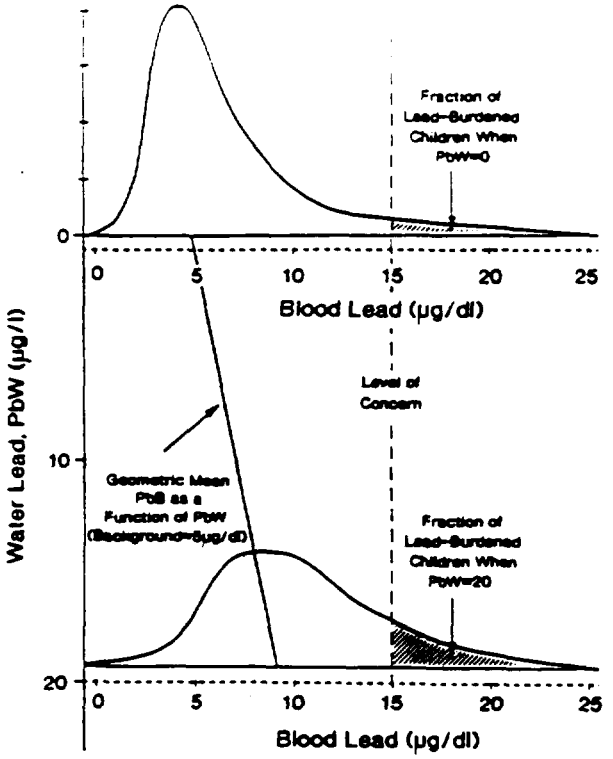

FIG. 6. Distribution of blood leads at different water lead values.

RESULTS

Effects of variability. The effect of blood lead variability on population risk is shown in Fig. 6. We illustrate the distribution of blood leads for two populations of children, one with a geometric mean blood lead of 5 mcg/dl and another with 10 mcg/dl. The larger geometric mean could be attributed to a difference in water lead levels (or dust or paint lead, etc.). Even with a modest GSD = 1.42, the fraction of children with elevated blood leads (above 15 mcg/dl) is many times greater in the second population than in the first. The increase in the fraction of children with elevated blood lead (EBL) shows a highly nonlinear increase with increasing mean blood lead. This is demonstrated in Table 8, where we have used the IEUBK model to estimate the percentages of EBL children as a function of both soil lead absorption fraction and GSD. Doubling the soil lead absorption parameter increases the EBL fraction by a much larger factor for almost all blood lead levels of concern.

The use of disaggregate models for lead abatement scenarios. To illustrate the importance of site-specific data in

TABLE 9
Input Parameters for Soil Lead Abatement Scenario

Preabatement			Postabatement	
Soil lead concn (µg/g)	Dust lead concn (µg/g)	Proportion of population	Soil lead concn (µg/g)	Dust lead concn (µg/g)
250	250	0.20	250	250
500	400	0.20	500	400
1,000	700	0.25	1000	700
2,000	1300	0.20	250	250
5,000	3100	0.10	250	250
10,000	6100	0.05	250	250
		Geom mean lead		
999	746		406.1	355.3
		Mean lead		
1800	1180		487.5	392.5

TABLE 8
Blood Lead Distributions for Alternative Soil Lead Absorption Parameters

	Soil lead absorbtion			
	15%[a]		30%[b]	
GSD:	1.42	1.66	1.42	1.66
Blood lead (L)	Percentage above L			
10 µg/dl	11.02	20.18	33.70	36.96
15 µg/dl	1.01	5.37	5.73	13.79
20 µg/dl	0.10	1.47	0.83	4.84
25 µg/dl	0.02	0.46	0.14	1.78

Note. Soil lead = 1000 µg/g, dust lead = 700 µg/g, children of ages 12–24 months using USEPA lead model.
[a] Geometric mean blood lead 6.64 µg/dl.
[b] Geometric mean blood lead 8.63 µg/dl.

TABLE 10
Blood Lead Distributions for Distributed Soil Lead Concentrations Using USEPA Lead Model

	GSD = 1.42	
	Preabatement	Postabatement
Percentage of children ages 12–24 months with blood lead >10 µg/dl		
Actual	41.85	9.07
Using geom mean lead	36.20	1.30
Using mean lead	83.51	2.68
	GSD = 1.66	
	Preabatement	Postabatement
Actual	42.88	12.54
Using geom mean lead	40.37	6.18
Using mean lead	75.02	9.14

abatement scenarios, we show the preabatement and postabatement distributions of soil lead in a hypothetical community in Table 9: 20% of the sites have soil leads of 250 μg/g, 20% have 500 μg/g, 25% have 1000 μg/g, 20% have 2000 μg/g, 10% have 5000 μg/g, and 5% have 10,000 μg/g. Dust lead was calculated as 0.6 (soil lead) + 100 μg/g. The geometric mean soil lead for the whole community is about 1000 μg/g, and the dust lead about 750 μg/g. The abatement scenario is site-specific. The 35% of the sites above 1000 μg/g soil lead are abated to 250 μg/g, and the other 65% of the sites with 1000 μg/g or less are not abated. This reduces the geometric mean soil lead to about 400 μg/g, and the dust lead to 355 μg/g.

The IEUBK model with all other standard default parameters was applied to the six separate population subgroups. The percentage of children with blood leads above 10 μg/dl was calculated for each subpopulation, multiplied by the percentage of sites at that level, and added up. The results are shown in Table 10. With an assumed GSD of 1.42, the soil lead abatement reduces the percentage of toddlers with blood leads above 10 μg/dl from 42% to only 9%. However, the majority of those above 10 μg/dl in the postabatement scenario come from the unabated sites with 1000 μg/g soil lead.

If average values of soil and dust lead had been used, the effectiveness of the abatement would have been greatly overestimated. If the IEUBK model were run with all sites having a preabatement soil lead of 999 μg/g and a postabatement soil lead of 406 μg/g (the actual geometric means), we would estimate that only 1.3% of the children would exceed 10 μg/dl postabatement, and so greatly overestimate the effectiveness of the abatement. The use of arithmetic mean rather than geometric mean soil leads changes the distortion of percentages and exaggerates the relative improvement even more so. The use of a more accurate GSD of 1.66 does not correct the situation. *The appropriate site-specific parameters for remediation effectiveness must be used.*

Additional approaches have been used in our studies of the cost effectiveness of paint and water lead abatement in U.S. urban areas (Marcus, 1990a; Revicki *et al.*, 1991). Paint lead abatement may not be perfectly effective, so the children in the paint-abated houses must be redistributed over a range of residual paint lead abatement risks. There is, unfortunately, little data that can be used to validate these models at present.

Discussion

The fraction of lead-exposed children with elevated blood lead levels (EBL) can be predicted using a computer simulation model based on realistic parameters of fetal and child development. This fraction does not depend linearly on changes in environmental lead concentrations or absorption parameters. Thus, the effectiveness of any environmental lead intervention or mitigation procedure must be disaggregated to the level of differences in either concentrations or populations within which the abatements are being carried out. "Average" abatements applied to "average" or "typical" sites or populations may give highly misleading estimates of the distribution of effectiveness of the mitigating actions. The populations at risk should be disaggregated according to their exposure parameters and remedial actions based on exposure levels. Since some lead abatement procedures have an effectiveness that varies over time, benefits of lead abatement must be calculated over sufficiently long intervals of time to cover these changes in effectiveness.

There are some real site-specific differences related to child and adult behavior, activity patterns, environmental pathways, and bioavailability. Sensitive parameters in these models should be adjusted to site-specific values, where known. A much greater level of guidance on the use or rejection of default parameters, and on the necessary level of site-specific information that must be collected to use the model appropriately, would greatly benefit site managers who must select appropriate cleanup levels for lead contamination.

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